2002-732783/79 B03 **SHIO 2001.03.01**
SHIONOGI & CO LTD *WO 200270491-A1
2001.03.01 2001-057036(+2001JP-057036) *(2002.09.12)* C07D 235/12, A61K 31/4184, 31/427, 31/437, 31/4439, 31/4725, 31/501, C07D 239/74, 241/42, 241/12, 487/04, 471/04, 417/06, 403/06, 401/06, 277/64, 277/24, 263/56, 513/04, 498/04, 263/32, 239/26, A61K 31/506, A61P 31/12, 31/18, 43/00, C07D 213/50

New nitrogenous heteroaromatic compounds are HIV integrase inhibitors for treating HIV infections, AIDS and AIDS related diseases (Jpn)

C2002-207360 N(AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW) R(AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW)

Addnl. Data: FUJI M
2002.02.27 2002WO-JP01779

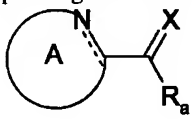
B(7-H, 14-A2B1, 14-D3, 14-G1B) .4

NOVELTY

Nitrogenous heteroaromatic compounds (I) are new.

DETAILED DESCRIPTION

Nitrogenous heteroaromatic compounds of formula (I) and their prodrugs salts and hydrates are new.



(I)

A = nitrogenous heteroaromatic;
X = O, S or NH;
R_a = $C(=Z_4)R_b$ or nitrogenous heteroaryl attached via an atom adjacent to N;
at least one of A and R_a = substituted by $Z_1Z_2Z_3R_1$ and both are optionally substituted by 1-6 Q;
Z_4 = O, S or NH;
R_b = H or Q;

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Z_1, Z_3 = bond or optionally substituted alkylene or alkenylene;
Z_2 = bond, CHOH, S, SO, SO_2, SO_2NR_2, NR_2SO_2, O, NR_2, NR_2CO, $CONR_2$, COO, OCO, CO or optionally substituted alkylene or alkenylene;
Q = halo, COOAlk, COOH, OAlk AlkOAlk, NO_2, OH, alkynyl, SO_2Alk, SAlk, AlkSAlk, haloalkyl, haloalkoxy, cycloalkyl, cycloalkenyl, oxo, thioxo, alkylenedioxy, alkylene, alkenylene, nitroso, N_3, amidino, guanidino, CN, NC, SH, SO_2NH_2, NH_2SO_2, CHO, COAlk, OCOAlk, hydrazino, morpholino or optionally substituted Alk, alkenyl, amino, $CONH_2$, Ar, heterocyclyl, AlkAr, OAr, SAr, OAlkAr, AlkOAr, AlkSAr, SO_2Ar or SO_2AlkAr;
Alk = alkyl;
Ar = aryl or heteroaryl.

ACTIVITY

Anti-HIV.
In assays a compound of formula (I-1) had an IC_{50} value for HIV integrase of 0.230 micro g/ml.

MECHANISM OF ACTION

HIV-Integrase-Inhibitor

USE

As HIV integrase inhibitors for treating and preventing HIV infections, AIDS and AIDS related diseases.

ADMINISTRATION

Dosage is 0.05-3000 (preferably 0.1-1000) mg/day orally or 0.01-1000 (preferably 0.05-500) mg/day parenterally. (I) may be administered with reverse transcriptase inhibitors and/or protease inhibitors.

EXAMPLE

1.5 M n-Butyl lithium in hexane (4.33 ml) was added at -65°C to a compound of formula (4) (2.25 g) in tetrahydrofuran (70 ml) and the mixture was stirred at -65°C for 1 hour then at -40°C for 30 minutes. Methyloxalyl chloride (0.920 ml) was added at -65°C and the mixture was stirred at -30°C for 30 minutes. Work-up including silica gel chromatography hexane:ethyl acetate (= 2:1) gave 628 mg (23%) of product which was deprotected using trifluoroacetic acid to give a compound of formula (I-1) in 82% yield.

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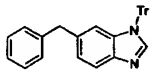
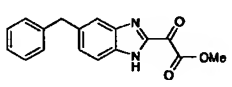


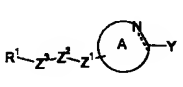
(4)



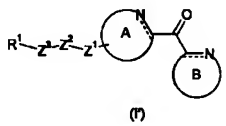
(I-1)

TECHNOLOGY FOCUS

Organic Chemistry - Preparation: (I) are prepared e.g. by acylating a heteroaromatic compound of formula (II) to give a compound of formula (I').



(II)



(I')

Y = H, Cl, Br or I.
(83pp2533DwgNo.0/0)

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